REMARKS

Claims 1-36, 38-39, 43-44 and 50-62 were previously cancelled without prejudice or disclaimer as to the claimed subject matter. Claim 37 is currently amended. Support for the amendment can be found throughout the specification as originally filed, *inter alia*, on page 13, line 23 through page 15, line 5, and page 17, lines 18-23. Claim 41 has been amended to correct a typographical error. Claims 37, 40-42, 45, 47-49, 63 and 64 are currently pending in the present application. Applicants respectfully request entry of the amendment, and reconsideration of the remaining pending claims.

Rejections Under 35 U.S.C. § 112, ¶ 1, Written Description

Claims 37, 40-42, 45, 47-49, 63 and 64 remain rejected under 35 U.S.C. § 112, ¶ 1 as allegedly failing to comply with the written description requirement. The Office Action incorrectly alleges: "The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention." Office Action, page 2. The Examiner appears to misapprehend the claimed applicable legal standard when she states that the specification does not teach a reagent that is useful in treating mammalian disease nor provide guidance as to the biological activity or structure of the reagent used in the claimed invention.

Applicants respectfully traverse the rejection. The Claims are fully supported in the specification as originally filed and a person of skill in the art would recognize that Applicants were in full possession of the application as claimed. Claim 37 was previously amended to recite that the intermediary metabolite is a *glycolipid*, and wherein the disease is *cancer, a viral infection, or an autoimmune disease*. It appears that the Examiner has not fully considered this amendment in formulating the present rejection. Nonetheless, in a further effort to advance the prosecution of the case, independent claim 37 is presently amended to recite a process for treating a disease in a mammalian subject comprising obtaining cells from the subject, treating the cells with an effective amount of an intermediary metabolite or a reagent that increases the intracellular level of a

mammalian intermediary metabolite in the cells, and transferring the treated cells to the patient. The intermediary metabolite or reagent is a glycolipid, and the disease is cancer, a viral infection, or an autoimmune disease.

In addition to repeating the rejection found in the previous Office Action, the Examiner further states that there is no teaching of biological activities or structural characteristics of the reagents in the specification. Contrary to the Examiner's statements, the specification does provide guidance or Examples as to the type of reagent used in the methods of the invention.

The present invention provides processes for treating disease in a mammalian patient by altering the intracellular levels of intermediate metabolites in cells obtained from the patient and then transferring the treated cells to the patient. This process provides at least one change in one or more components of the immune system. The change may occur directly or indirectly. Direct means includes introduction of the *metabolite itself* into the subject. See specification, page 7, lines 1-9. The specification further describe how the metabolite or reagent which affects the levels of the metabolite may be introduced by various methods including ex vivo procedures (page 13, lines 3-9) and further teaches how intermediary metabolites can be used to treat various diseases, such as cancer and immune-mediated pathogenic conditions. An example is given showing how one such disease (small cell carcinoma of the lung) may be treated with an intermediary metabolite (glucosylceramides). Page 13, line 23 through page 14, line 10. The specification continues with a detailed description of "A Further Embodiment of the Invention" in which an effective amount of a mammalian intermediary metabolite or reagent is administered to a subject, thus raising the serum level of the metabolite in the subject. A listing of different types of intermediary metabolites then follows. Page 14, line 22 through page 16, line 5.

The specification clearly teaches that an intermediary metabolite can fulfill the role of a reagent. Applicants describe one important property of a reagent as the ability to raise the serum or intracellular levels of an intermediary metabolite in a subject. An intermediary metabolite itself can perform this function and, as described in the passages

cited above, the intermediary metabolite can act as the reagent. Administration of the intermediary metabolite effectively rises the serum and intracellular levels of the intermediary metabolite. Thus, the Examiner's contention that there is no teaching of biological activities or structural characteristics of the reagents or intermediary metabolites in the specification is incorrect.

The specification adequately describes that glycolipids are useful as intermediary metabolites or reagents in the recited methods. For instance, the specification provides that glucosylceramides (an intermediary metabolite) may be used to treat, for example, cancer, infectious diseases, and any immune-mediated pathogenic condition as follows:

> Intermediary metabolites, such as glucosylceramides, can be used in accordance with this invention to treat various diseases, including cancer, infectious diseases and any immune-mediated pathogenic condition. For example in the instance of small cell carcinoma of the lung, subjects can be treated by administration of glucosylceramides such that at least one component of the immune system is elevated to such an extent that a specific activation of the NKT cell population is effected. Under these conditions the immune response to the cancer will be altered in such a manner that the cancer cells will be turned over or destroyed or lead to be destroyed and the subject will enter remission or experience a significant diminution of the cancer. A comparable effect can also be achieved by removing NKT cells from the subject and exposing these cells to glucosylceramides in vitro under conditions that will permit the survival and growth of the cells. When these ex vivo-trained cells are transferred back into the subject these cells will direct an immune response that can lead to a remission of the cancer or a significant diminution of the cancer.

See specification at paragraph spanning pages 13 and 14.

The passage quoted above specifically describes how the introduction of an effective amount of a specific intermediary metabolite useful in treating a disease (a glucosylceramide used to treat a cancerous condition) possesses a specific biological activity (elevation of an immune component) which results in a specific manner (activation of the NKT cell population).

The specification provides further guidance as to the structure of the intermediary metabolite (the glycolipid) at the top of page 15: "Such glycolipids can in turn comprise a monosaccharide ceramide, *e.g.*, glucosyl ceramide or gala(c)tosyl ceramide." On the

lower part of page 15, the specification states: "The glycolipids can comprise a monosaccharide ceramide. Preferred are glucosyl ceramide or gala(c)tosyl ceramide."

It also appears that The Examiner unfortunately misapprehends the legal standard for written description and thus fails to correctly apply the law. The Examiner appears to cling to the incorrect notion that structure is required for an adequate written description of a biological macromolecule. That viewpoint, however, was laid to rest last year in *Falkner v. Inglis*, 448 F.3d 1357 (Fed. Cir. 2006). In that case, the Federal Circuit considered whether claims directed to a vaccine comprising a mutant poxvirus were adequately described by Inglis' specification. The Court enunciated the following written description principles: (1) examples are not necessary to support the adequacy of a written description, (2) the written description standard may be met even where actual reduction to practice of an invention is absent, and **(3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure.** As the Court pointed out, it is binding precedent of the Federal Circuit that *Eli Lilly* does not set forth a ***per se*** rule that whenever a claim limitation is directed to a macromolecular sequence, the specification must always recite the gene or sequence.

Applicants therefore respectfully submit that amended claim 37 recites a specific description of the particular kind or type of intermediary metabolite that could be used as a reagent. Moreover, the claims dependent from claim 37 recite monosaccharide ceramide and specifically glucosyl ceramide and galactosyl ceramide, which provide further structural definitions with regard to the particular reagents (intermediary metabolites) recited by the present claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection in view of the above amendment.

Rejection Under 35 U.S.C. § 112, ¶ 1, Enablement

Claims 37, 40-42, 45, 47-49, 63 and 64 are rejected under 35 U.S.C. § 112, ¶ 1 as allegedly failing to comply with the enablement requirement. The Office Action states

that "The specification does not provide any guidance directing the type or kind of reagent that the skilled artisan should use to treat mammalian disease." Office Action page 9. Applicants respectfully traverse the rejection.

The claims are directed to a process for treating a disease in a mammalian subject comprising obtaining cells from the subject, treating the cells with an effective amount of an intermediary metabolite or a reagent that increases the intracellular level of a mammalian intermediary metabolite in the cells, and transferring the treated cells to the patient. The intermediary metabolite or reagent is a glycolipid, and the disease is cancer, a viral infection, or an autoimmune disease. The Examiner bases the rejection on the assertion, as stated above, that the specification does not contain enough guidance as to the type or kind of reagent used in the methods of the invention. As described in detail above, the use an intermediary metabolite fulfills the role of a reagent in the process of the present invention. Administration of the intermediary metabolite effectively raises the intracellular levels of the intermediary metabolite in the treated cells. Applicants previously submitted that the specification teaches that patients suffering from Gaucher's Disease display a natural buildup of monosaccharide ceramides, an intermediary metabolite. This buildup provides beneficial results with regard to immune responses to HCV infection. The Examiner questions the asserted beneficial result. In response, Applicants respectfully direct the Examiner's attention to the paragraphs starting at page 9, line 3 and continuing to page 13, line 3 and Figs. 1-6. These experiments describe the significant impact of the increased metabolite level on the immune profile of HCV positive subjects. Page 12, lines 10-13. Specifically, the increase in monosaccharide ceramides resulted in changes in HCV specific T-cell proliferation (Fig. 1); HCV specific IFNγ levels (Fig. 2); HCV specific IL-10 levels (Fig. 3); IFNγ serum levels (Fig. 4); IL-4 serum levels (Fig. 5) and peripheral NKT lymphocyte levels (Fig. 6). Thus, the specification clearly illustrates the beneficial result of the increased level of an intermediary metabolite in those suffering from Gaucher's Disease and HCV infection.

Contrary to the Examiner's assertion that there is limited guidance in the specification, the specification provides guidance as to the types of disease to which the present invention applies in the form of Examples. At the very least, examples of the

present specification clearly set forth a protocol for testing the effects of the intermediary metabolite (monosaccharide ceramides) on the immune profile of patients suffering from HCV infection, which amounts to adequate guidance without requiring an unreasonable amount of experimentation. See MPEP § 2164.02 (absence of working examples will not by itself render the invention non-enabled).

The Examiner continues by reciting the rejection articulated in the previous Office action to support the contention that the specification is not enabled. Specifically, the Examiner states that independent claim 37 is very broad in encompassing all diseases, all mammalian subjects, all reagents and all intermediary metabolites. The claims recite a process for treating a disease in a mammalian subject utilizing an intermediary metabolite that is a glycolipid. Furthermore, the claims recite a disease that is cancer, a viral infection, or an autoimmune disease. There is no question that a person of skill in the art would be able to utilize the recited metabolite for treatment of the recited diseases.

The Examiner further contends that the lack of working Examples renders the present specification nonenabling. As noted above, the absence of working examples will not by itself render the invention non-enabled. See MPEP § 2164.02.

The Examiner then states that besides the association between various immunoparameters in subjects diagnosed with Gaucher's Disease as compared to patients also diagnosed with HCV, the specification does not provide any additional guidance pertaining to the relevance of the observations described in the Examples. The Examiner then concludes that one of skill in the art could not rely on the disclosure set forth in the specification to practice the invention without undue experimentation. The Examiner contends that the skilled artisan would have to blindly experiment with each known disease, metabolite and reagent.

Applicants respectfully submit that the Examiner misapprehends the enablement requirement. It is well established under 35 U.S.C. §112 ¶ 1, that, "[t]he test of enablement is not whether any experimentation is necessary, but whether, if

experimentation is necessary, it is *undue*." MPEP 2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976) (Emphasis added).

As explained above, the claims as presently amended recite a specific class of intermediary metabolites. In addition, the specification provides adequate guidance to one of skill in the art to practice the recited process for the treatment of cancer, viral infection, or autoimmune disorder (specific diseases) without undue experimentation. Thus, no "blind experimentation" to determine metabolites, reagents or diseases is necessary.

In addition, the specification discloses that Gaucher's patients display a natural buildup of monosaccharide ceramides that produces beneficial results with regard to immune responses to HCV infection. The specification also provides that the same buildup may be created in a non-Gaucher's patient to achieve the same or similar beneficial outcome. Furthermore, the specification provides examples as to the types of disease where the present invention and the resulting beneficial effects are applicable, *e.g.*, cancer, viral infections, and immune dysfunctions. Specific reference is made to using an intermediary metabolite for treating HBV, HCV, or HIV infection on page 12 of the specification; treatment of small cell carcinoma of the lung with glucosylceramide on page 13; and treatment of autoimmune diseases such as diabetes type I, diabetes type II, rheumatoid arthritis, Crohn's disease, arteriosclerosis and ulcerative colitis on page 14. Thus, the specification provides adequate guidance as to the type of intermediary metabolite to be used and the type of disease to be treated.

With regard to immune dysfunction diseases, the specification notes the utility of the present invention in autoimmune diseases where there is an inappropriate response to native cells. Moreover, as stated on page 14 of the specification: "The present invention can also be applied to management of cancers, where the immune response contributes to the pathogenesesis." Development of cancer is considered a product of some defect in what is commonly termed "immune surveillance." In other words, not only is there some aberration in the cancer cells that have resulted in their transformation, but also a failure in the immune system to recognize the presence of these abnormal cells.

Consistent with the above disclosures, claim 37 recites that the disease to be treated is cancer, a viral infection or an autoimmune disease. Claim 37 further recites a glycolipid as the mammalian intermediary metabolite, and claims 40 and 41 recite monosaccharide ceramide, glucosylceramides and galactosylceramide. Given the level of skill in the art, the breadth of the claims, the presence of examples, the amount of direction or guidance presented and the quantity of experimentation necessary, the claims are fully enabled by the specification as filed. Applicants respectfully request withdrawal of this rejection.

CONCLUSION

A petition for a three-month extension of time and the required fee are being transmitted concurrently with this submission. A Request for Continued Examination under 37 C.F.R. § 1.114 and the required fee are being transmitted concurrently with this submission as a separate paper. In the event that additional fees are deemed necessary, or in the event of any variance between the amount enclosed and the fees determined by the USPTO, please charge or credit any such variance to the undersigned's Deposit Account No. 50-0206.

In view of at least the foregoing, Applicants respectfully submit that the claims are in condition for allowance. Early notification of a favorable consideration is respectfully requested. In the event any issues remain, Applicants would appreciate the courtesy of a telephone call to their counsel at the number listed below to resolve such issues and place all claims in condition for allowance.

Respectfully submitted,

HUNTON & WILLIAMS LLP

Dated: June 15, 2007

By: Kellie L Carden

Robert M. Schulman
Registration No. 31,196
Scott F. Yarnell
Registration No. 45,245
Kellie L. Carden
Registration No. 52,696

HUNTON & WILLIAMS LLP
Intellectual Property Department
1900 K Street, N.W., Suite 1200
Washington, DC 20006-1109
(202) 955-1500 (telephone)
(202) 778-2201 (facsimile)